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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte NOBUTO YAMAMOTO

Appeal 2007-3910
Application 09/826,463
Technology Center 1600

Decided: January 25, 2008

Before DONALD E. ADAMS, DEMETRA J. MILLS,
and LORA M. GREEN, Administrative *Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims 22 and 24, the only claims pending in this application. We have jurisdiction under 35 U.S.C. § 6(b).

INTRODUCTION

The claims are directed to a process of producing a cloned macrophage activating factor (GcMAFc)¹. The claims are reproduced below:

22. A process for producing a cloned macrophage activating factor (GcMAFc) comprising:

- (a) cloning a Gc1 isoform into a baculovirus vector;
- (b) expressing the cloned Gc1 isoform, thereby producing a cloned Gc1 protein, wherein the Gc1 protein comprises approximately 458 amino acids with a molecular weight of approximately 52,000 Da and 3 distinct domains;
- (c) contacting the cloned Gc1 protein with immobilized beta galactosidase and sialidase; and
- (d) obtaining the cloned macrophage activating factor (GcMAFc).

24. A process for producing a functional cloned macrophage activating factor (GcMAFc) comprising:

- (a) cloning a Gc1 isoform into a baculovirus vector;
- (b) expressing the Gc1 isoform, thereby producing a cloned Gc1 protein, wherein the cloned Gc1 protein comprises approximately 458 amino acids with a molecular weight of approximately 52,000 Da and 3 distinct domains;
- (c) sequencing the cloned Gc1 peptide, thereby confirming that the cloned Gc1 protein is a cloned wild type Gc1 protein;

¹ Appellant defines “GcMAFc” as “cloned Gc protein-derived macrophage activating factor” (Specification 2: 10). Appellant defines “GcMAF” as “Gc protein-derived macrophage activating protein” (Specification 2: 9). Thus, the only difference between GcMAF and GcMAFc is whether the protein is recombinantly produced (GcMAFc) or not (GcMAF).

- (d) contacting the cloned wild type Gc1 protein in vitro with immobilized beta galactosidase and sialidase; and
- (e) obtaining the cloned wild type macrophage activating factor (GcMAFc).

The Examiner relies on the following prior art references to show unpatentability:

Yamamoto	US 5,177,002	Jan. 5, 1993
Murphy	US 5,516,657	May 14, 1996
Lichenstein	US 5,652,352	Jul. 29, 1997

Cooke, *Serum Vitamin D-binding Protein is a Third Member of the Albumin and Alpha Fetoprotein Gene Family*, 76(6) Jour. Clin. Invest. 2420-2424 (1985).

Quirk, *Production of Recombinant Human Serum Albumin from Saccharomyces Cerevisiae*, 11 Biotechnology and Applied Biochemistry 273-287 (1989).

Lu, *Isolation and Characterization of Three Recombinant Human Granulocyte Colony Stimulating Factor His Gln Isoforms Produced in Escherichia Coli*, 4 Protein Expression and Purification 465-472 (1993).

Luckow, *Protein Production and Processing From Baculovirus Expression Vectors, in Baculovirus Expression Systems and Biopesticides*, 51-90 (Michael L. Shuler et al. eds., John Wiley & Sons, Inc. 1995).

The rejections as presented by the Examiner are as follows:

1. Claim 24 stands rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written descriptive support.
2. Claim 22 stands rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Yamamoto, Cooke, Quirk, Lichenstein, Murphy, and Luckow.
3. Claims 22 and 24 stand rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Yamamoto, Cooke, Quirk, Lichenstein, Murphy, Luckow, and Lu.

We affirm.

DISCUSSION

New Matter:

1. Claim 24 stands rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written descriptive support.

According to the Examiner “[s]upport for the limitation ‘sequencing the cloned Gc1 isoform, thereby . . . wild type Gc1 isoform;’ (step (c) of claim 24) cannot be found in the originally filed disclosure, which raises the issue of new matter” (Answer 3). According to Appellant, this language was added to claim 24 by amendment on July 11, 2005 (Br. 4).

Directing attention to page 10, lines 5-7 of the Specification, Appellant asserts that “the Specification as filed discloses that Appellant was able to determine, using chemically and proteolytically fragmented Gc, that the smallest domain, domain III contains an essential peptide for macrophage activation” (Br. 4). In this regard, we note that Appellant’s discloses:

Domain I interacts with vitamin D while domain III interacts with actin (Haddad *et al.*, Biochem., 31:7174, 1992). Chemically and proteolytically fragmented Gc enabled me to indicate that the smallest domain, domain III, contains an essential peptide for macrophage activation. Accordingly, I cloned both Gc protein and the entire domain III peptide, by the use of a baculovirus vector and an insect host, and treated them with the immobilized β -galactosidase and sialidase to yield potent macrophage activating factors, designated GcMAFc and CdMAF, respectively. Like GcMAF, these cloned GcMAFc and CdMAF appear to have curative effects on cancer.

(Specification 10: 4-11.) According to Appellant the Haddad reference was cited at page 10, lines 4-5 of the Specification “and incorporated by reference in its entirety (Specification at page 28, lines 1-2)” (Br. 4). Page 28, lines 1-2 of Appellant’s Specification states “[t]he following references are cited and their entire text is incorporated fully herein as are all references set forth above in the Specification” (Specification 28:1-2).

Appellant asserts that Haddad “teaches that it was known in the art to sequence peptides of native serum Gc protein” (Br. 4.). Appellant asserts that Haddad “teaches the sequencing of Gc peptide (i.e., DBP) and comparison to known, wild-type (hDBP) protein. The limitation in claim 24 subsection (c) is directed to sequencing of the Gc protein to determine whether it is wild-type. This is exactly what the Haddad reference shows” (Br. 5).

Thus, Appellant argues that

[t]he information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed. Replacing the identified material incorporated by reference with the actual text is not new matter.

(Br. 6.)

“To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and *clearly indicate where that material is found in the various documents.*” *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) (emphasis added), citing *In re Seversky*, 474 F.2d 671, 674 (CCPA 1973) (To incorporate another document by reference, the host document must “clearly identify[] the subject matter which is incorporated and where it is to be found.”), and *In re Saunders*, 444 F.2d 599, 602-603 (CCPA 1971) (reasoning that a rejection for anticipation is appropriate only if one reference “*expressly incorporates a particular part*” of another reference.) (emphasis added); Manual of Patent Examining Procedure (MPEP) § 608.01(p) (7th ed., rev. 1, Feb. 2000)²) (“Particular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found.”).

Thus, in order to incorporate material by reference, an applicant must not only (1) identify the material to be incorporated, but must also (2) clearly indicate where that material is found in the document. While Appellant makes a blanket statement that all references set forth in the Specification are incorporated in their entirety, Appellant identifies only a portion of Haddad with any particularity, specifically that Haddad teaches that “[d]omain I interacts with vitamin D while domain III interacts with actin” (Specification 10: 4-5). As the Examiner explains, “this portion of the [S]pecification only refers to Haddad in regard to determining the functional domains of the Gc protein. Thus, it is not clear that [A]ppellant intended to

² This revision of the MPEP was in effect as of the April 5, 2001 filing date of Appellant’s Specification.

incorporate by reference Haddad's sequencing procedure" (Answer 6). We agree.

In this regard, the Examiner finds that Appellant's Specification indicates that [A]ppellant chemically and proteolytically fragmented Gc and determined that domain III contained an essential peptide for macrophage activation and then cloned both Gc protein and the entire domain III peptide, by the use of a baculovirus vector and an insect host. The [S]pecification does not indicate that [A]ppellant cloned Gc protein, . . . proteolytically fragmented Gc, assembled the entire Gc protein sequence from overlapping peptide sequences, and compared that sequence to a wild-type sequence.

(Answer 6-7.) According to the Examiner,

[a]t best it might have been obvious to the skilled artisan that it would be desirable to determine the amino-terminal sequence of a chemical or proteolytic fragment of the Gc protein in order to determine the chemical or proteolytic cleavage sites, and hence the location of the fragment. However, the written description [requirement] does not extend to subject matter which is not disclosed, but would [have] be[en] obvious over what is expressly disclosed. It extends only to that which is disclosed. One shows that one "had possession" of the invention by describing the invention, with all its claimed limitations, not that which makes it obvious.

(Answer 6.) We agree. *See Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571-72 (Fed.Cir.1997) ("The question [of adequate written description] is not whether a claimed invention is an obvious variant of that which is disclosed in the specification.")

Part (c) of claim 24 requires that the cloned Gc1 peptide is sequenced to confirm that the cloned Gc1 protein is a cloned wild type Gc1 protein. Appellant has failed to identify with any particularity where this specific

limitation finds support in their originally filed Specification. In our opinion, that “Appellant was able to determine, using chemically and proteolytically fragmented GC, that the smallest domain, domain III contains an essential peptide for macrophage activation” is insufficient to support the sequencing limitation in part (c) of claim 24 (Br. 4).

We are also not persuaded by Appellant’s assertion that

the relevant portion of Haddad . . . teaches sequencing of the Gc peptide (also known as DBP) is on p. 7175, column 2, ¶2:

For peptides correlating with radioactivity in paired gel lanes, their stained membrane bands were isolated with a razor blade and were analyzed for amino-terminal sequence The results obtained were compared with the known sequence of hDBP

Thus Haddad, . . . teaches the sequencing of Gc peptide (i.e., DBP) and comparison to known, wild-type (hDBP) protein.

(Br. 5 (emphasis removed).) Contrary to Appellant’s intimation, the Examiner explains that “the amino-terminal sequence of proteolytic fragments of the native hDBP would not confirm that the native hDBP is a wild type protein because the identity of the rest of the amino acid sequence of the native hDBP was unresolved” (Answer 8). Therefore, even had Appellant properly incorporate this portion of Haddad by reference, Appellant still fails to support the limitation in part (c) of claim 24 that requires the cloned Gc1 peptide to be sequenced to confirm that the cloned Gc1 protein is a cloned wild type Gc1 protein.

For the foregoing reasons we affirm the rejection of claim 24 under the written description provision of 35 U.S.C. § 112, first paragraph.

Obviousness:

2. Claim 22 stands rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Yamamoto, Cooke, Quirk, Lichenstein, Murphy, and Luckow.

The Examiner finds that “Yamamoto teaches a process of converting glycosylated Gc protein (Gc1 isoform) to a highly potent macrophage activating factor (GcMAF) by contacting Gc protein with immobilized beta-galactosidase and sialidase” (Answer 9). The Examiner finds that “Yamamoto refers to Cooke . . . for [the] nucleotide and amino acid sequences of Gc protein” (Answer 10). According to the Examiner “Cooke’s sequence represents the Gc1 allele” (*id.*). The Examiner finds that both Yamamoto and Cooke teach that “[t]he Gc protein has a molecular weight of about 52,000, comprises approximately 458 amino acids, and has three distinct domains” (*id.*).

The Examiner finds that Yamamoto differs from Appellant’s claimed invention by isolating “the Gc protein from human blood” rather than “producing the Gc protein via recombinant DNA technology and converting the recombinantly produced Gc protein to GcMAF” (*id.*). However, with reference to Quirk, the Examiner finds that “[t]he concern about human viral contamination in products purified from blood may be avoided if these products are obtained via recombinant DNA technology” (*id.*). In this regard, the Examiner relies on Lichenstein, Murphy, and Luckow to teach the advantages of the Baculovirus system to clone genes and express recombinant proteins (Answer 11-12).

Based on this evidence, the Examiner finds that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of Appellant’s invention to recombinantly produce a Gc1 in a Baclovirus

system, contact the recombinantly produced Gc1 isoform in vitro with immobilized beta-galactosidase and sialidase, and obtain GcMAF (Answer 12). According to the Examiner, “[o]ne of ordinary skill in the art would be motivated to make this modification because the concern about human viral contamination in products purified from blood may be avoided if these products are obtained via recombinant DNA technology” (*id.*).

We find no error in the Examiner’s *prima facie* case of obviousness.

In response, Appellant asserts that since Yamamoto did not produce the Gc isoform recombinantly, Yamamoto only produced GcMAF and not GcMAFc (Br. 7). We are not persuaded by this argument. The combination of references relied upon by the Examiner not only teaches the recombinant production of the claimed Gc isoform and its subsequent conversion to GcMAFc, but also provides a persuasive rationale for doing so – specifically, to reduce the possibility of human viral contamination by using proteins that are not isolated from human blood.

According to Appellant, “only the cloned Gc1 protein having the wild type peptide sequence (Figure 3 of the instant application) is used to generate GcMAFc. Thus, the cloned Gc protein has to be sequenced, and have the sequence as shown in Figure 3” (Br. 8). We are not persuaded by Appellant’s argument. There is no requirement in claim 22 that the Gc1 protein has any particular sequence. Further, there is no showing on this record that Cooke’s sequence is distinct from the sequence set forth in Appellant’s Figure 3. While Appellant points out that Cooke never expressed the cloned cDNA for the Gc1 protein, Appellant fails to provide any evidence that Cooke’s predicted amino acid sequence is distinct from the Gc1 protein set forth in claim 22.

Appellant asserts that while Lichenstein demonstrates that an albumin like protein can be expressed in insect cells, e.g., a baculovirus system, Lichenstein does not show that Gc1 can be expressed in a baculovirus system (Br. 9). According to Appellant, “Gc protein is very different from other albumin family proteins, and . . . there is no teaching or suggestion in [Lichenstein] . . . of the expression and isolation of any and all albumin like proteins . . .” (Br. 10). Therefore, Appellant concludes that the combination of Yamamoto, Cooke and Lichenstein fails to “suggest a method of cloning Gc1 in baculovirus vector, expression of a cloned Gc1 protein in a baculovirus expression system, or contacting cloned Gc1 expressed in a baculovirus system with immobilized β-galactosidase and sialidase” (*id.*). Appellant makes similar arguments for both Murphy and Luckow (Br. 11). We disagree. There is no evidence on this record to suggest that Cooke’s Gc1 protein could not be expressed in a baculovirus system and contacted with immobilized β-galactosidase and sialidase as done with the biochemically isolated Gc1 protein taught by Yamamoto to produce GcMAFc (*Cf.* Answer 17-19 and 21). The baculovirus system is an eukaryotic expression system; there is no evidence on this record that an eukaryotic protein, such as Gc1, would not be post-translationally modified, e.g., sialylated, in the baculovirus system. Accordingly, we are not persuaded by Appellant’s assertion that “[t]here is no evidence in Murphy to suggest that a sialylated protein could be generated as easily due to the nature of the protein” (Br. 11 and 14).

According to Appellant, “[m]any secreted and membrane proteins produced in the baculovirus expression system frequently form insoluble aggregates or are improperly processed” (Br. 14). Appellant fails to direct

our attention to any evidence on this record to support this position. Further, Appellant fails to explain why a person of ordinary skill in the art would expect that the expression of Cooke's Gc1 protein in a baculovirus system would result in an improperly processed, insoluble aggregate (*Cf.* Answer 23). Accordingly, we are not persuaded by Appellant's argument. Similarly, we are not persuaded by Appellant's assertion that "some recombinant proteins are extensively degraded" when expressed in the baculovirus system (Br. 14-15).

"Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *Graham vs. John Deere Co.*, 383 U.S. 1, 17 (1966). To paraphrase *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007), if a technique has been used to improve one compound, and a person of ordinary skill in the art would recognize that it would improve similar compounds in the same way, using the technique is obvious unless its actual application is beyond his or her skill. On reflection, we conclude that the Examiner has properly applied the *Graham* factors and the cited references provide a reason to combine their teachings. Accordingly, we affirm the rejection of claim 22 under 35 U.S.C. § 103 as being unpatentable over the combination of Yamamoto, Cooke, Quirk, Lichenstein, Murphy, and Luckow.

3. Claims 22 and 24 stand rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Yamamoto, Cooke, Quirk, Lichenstein, Murphy, Luckow, and Lu.

The Examiner relies on the combination of Yamamoto, Cooke, Quirk, Lichenstein, Murphy, and Luckow as discussed above. Appellant did not

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separately argue the claims; therefore they stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Having found claim 22 prima facie obvious under 35 U.S.C. § 103 over the combination of Yamamoto, Cooke, Quirk, Lichenstein, Murphy, and Luckow. We do not address the Lu reference relied upon to teach “the analytical technique of protein sequencing” - a limitation of claim 24 (Answer 24).

Accordingly, we affirm the rejection of claim 22 under 35 U.S.C. § 103 as being unpatentable over the combination of Yamamoto, Cooke, Quirk, Lichenstein, Murphy, Luckow, and Lu. Claim 24 falls together with claim 22.

CONCLUSION

In summary, we affirm all rejections of record.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

dm

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